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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,934	12/31/2003	Thomas E. Tarara	0101.00	1899

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,934	TARARA ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-102* is/are pending in the application.

4a) Of the above claim(s) *23-37 and 84-102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 38-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/31/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/07 and 11/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the reply filed on 4/19/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The requirement is still deemed proper and is therefore made FINAL. The election of the following species is also acknowledged: phospholipids.

Claims 1 – 102 are pending, of which claims 23 – 37 and 84 – 102 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1 – 22 and 38 – 83 are readable upon the elected invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 8, 12 – 15, 19, 20, 38 – 44, 46 – 49, 52, 69 – 75, 77 – 79 and 82 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 7, 11, 12, 14 – 20 and 23 – 30 of copending Application No. 11/187,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to pharmaceutical formulations for pulmonary administration comprising particulates comprising an active agent particle wherein the active agent has a solubility in water of less than 1.0 mg/ml (amphotericin) in a lipid matrix, wherein at least 90% of the active agent particles in the pharmaceutical formulation have a geometric diameter less than 3 micrometers and wherein the particulates have a mass median diameter less than 20 micrometers. Accordingly, they are overlapping in scope and are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 – 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Weers *et al.* (WO 99/16422), as evidenced by Block (*J. Pharm. Sci.*, 1973, 62 (4), p. 617 – 621 (abstract)).

Weers discloses stabilized dispersions for the delivery of a bioactive agent to the respiratory tract of a patient (abstract). The stabilized preparations provide uniform dose delivery by metered dose inhalers through the use of hollow and/or porous perforated microstructures (page 4, lines 1 – 15). The dispersions or powders of the present invention may be used in conjunction with metered dose inhalers, dry powder inhalers, atomizers, nebulizers or liquid dose instillation (LDI) techniques to provide for effective drug delivery (page 4, lines 20 – 25). Weers teaches methods for the pulmonary delivery of one or more bioactive agents comprising the steps of providing a powder comprising a plurality of perforated microstructures having a bulk density of less than about 0.5 g/cm^3 wherein said perforated microstructure powder comprises a bioactive agent; aerosolizing said perforated microstructure powder to provide an aerosolized medicament; and administering a therapeutically effective amount of said aerosolized medicament to at least a portion of the nasal or pulmonary passages of a patient in need thereof. In addition to the bioactive agent, the compositions further comprise a surfactant, which is preferably a phospholipid. Exemplary phospholipids useful in the stabilized preparations include dipalmitoylphosphatidylcholine,

disteroylphosphatidylcholine, etc. (page 17, lines 15 – 30). The compositions are prepared by spray drying preparations comprising a surfactant such as a phospholipid and at least one active or bioactive agent, including in the presence of various calcium salts (page 26, line 5 – 13). The mean geometric particle size of the resulting perforated microstructures is preferably about 0.5-50 μm, more preferably 1-30 μm (page 14, lines 5 – 15). The compositions yield powders with bulk densities less than 0.5 g/cm^3 or 0.3 g/cm^3, preferably less 0.1 g/cm^3 and most preferably less' than 0.05 g/cm^3. The mean aerodynamic diameter of the perforated microstructures is preferably less than about 5 μm, more preferably less than about 3 μm, and, in particularly preferred embodiments, less than about 2 μm (page 15, lines 1 – 10). A particular bioactive agent which is exemplified includes triamcinolone acetonide (page 35, line 30+).

Although only one reference should normally be used in making a rejection under 35 U.S.C. § 102, such a rejection made utilizing multiple secondary references has been held to be proper when the extra references are merely cited to show that a characteristic not explicitly disclosed in the primary reference is inherent therein. See MPEP 2131.01 Multiple Reference 35 U.S.C. § 102 Rejections.

In the instant case, Block is included to demonstrate that the solubility of triamcinolone acetonide in aqueous media is inherently less than 1.0 mg/ml, as claimed. For example, triamcinolone acetonide has a solubility in distilled water ranging from 21 μg/ml at 28 °C to 33.6 μg /ml at 50 °C (abstract).

Claims 1 – 5, 7, 8, 12 – 15, 17, 18, 20 – 22, 38 – 44, 46 – 49, 51, 53, 69 – 75, 77 – 79, 81 and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim (Drug Delivery, 2001, 8(3), p. 143 - 147).

Kim discloses a potent drug carrier for systemic fungal infections, amphotericin B (AmB)-phospholipid composite particles (APCPs), which were prepared by the spray drying method (abstract). The phospholipid employed in the compositions include egg phosphatidyl choline (page 143). Spray-dried APCPs were determined to be spherical and the diameter was submicron, ranging from 0.1–1 micrometers as determined by TEM measurements (page 145). Regarding the limitation of claims 1, 15, and 17 wherein the pharmaceutical formulation is "for pulmonary administration" or "for aerosolization in a dry powder inhaler" or "for aerosolization in a nebulizer" it is respectfully noted that the intended use of the composition has not been given patentable weight to distinguish over Kim because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Kim discloses compounds that are the same as those claimed, they would be capable of performing the intended use, as claimed.

It is further noted that Kim does not specifically recite the mass mean diameter, bulk density, or crystallinity of the particles. Regarding the claimed properties, the Office does not have the facilities for examining and comparing applicant's product with

the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The mass mean diameter, bulk density and crystallinity are descriptive and thus would be inherent properties of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Kim discloses particles comprising amphotericin and phospholipids which are prepared by spray-drying, and which are within the size range of the claimed particles, it is interpreted that they would inherently have a mass mean diameter, bulk density, and crystallinity as claimed.

Claims 1 – 8, 12 – 18, 38 – 44, 46 – 51, 69 – 75 and 77 – 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Knight *et al.* (US 5,049,388).

Knight discloses aqueous aerosol droplets containing one or more liposome particles, the majority of the mass of the aerosol droplets having a diameter from 1 to 5 microns and having an aerodynamic mass mean diameter ranging from about 1 to 3 microns, the liposomes being substantially homogenous in size and having a diameter of less than 1 micron thereby providing deposition of the droplets containing the one or more liposome particles throughout a respiratory tract of a patient when inhaled (claim 1). The liposomes further comprise a medicament, including amphotericin (Table 1 or

Table 5). Specific phospholipids suitable for use in the compositions include dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, etc. (column 8, lines 30+). The liposomes may be processed by an aerosol nebulizer, propelled by air or oxygen-enriched air from heterogeneous sizes to substantially uniform small particle liposomes (column 4, lines 13+). It is noted that Knight does not specifically recite the bulk density or crystallinity of the particles. Regarding the claimed properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The bulk density and crystallinity are descriptive and thus would be inherent properties of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Knight discloses particles comprising amphotericin and phospholipids which are within the size range of the claimed particles, it is interpreted that they would inherently have a bulk density and crystallinity as claimed.

Claims 1 – 22 and 38 – 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Weers et al. (US 2002/0017295)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Weers discloses aerosolized pharmaceutical formulations for drug delivery to the lungs (paragraphs 0004 – 0005). The compositions comprise phospholipids and an active agent, including amphotericin B (paragraph 0014, 0019, claim 17). Specific phospholipids suitable for use include dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, etc. (paragraph 0036). The medicaments are formulated in such a way that it readily disperses into discrete particles with a mass mean diameter between 0.5 to 20 μm, may be spray-dried, hollow and porous, and have bulk densities less than 0.5 g/cm^3, preferably less than 0.1 g/cm^3 (paragraphs 0046 – 0050). The compositions include a polyvalent cation (paragraph 0062).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 22 and 38 – 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weers *et al.* (WO 01/85136) in view of Cicogna *et al.* (*Antimicrobial Agents and Chemotherapy*, 1997, 41 (2), p. 259 – 261).

Weers discloses phospholipid-based powders for drug delivery applications. The powders are hollow and porous and are preferably administered via inhalation (abstract). The phospholipid may be delivered alone or in combination with an active agent (page 4, lines 1 – 11). The active agent may be a variety of drugs, including amphotericin (page 6, line 32). The formulations include polyvalent cations in the manufacture of phospholipid-containing dispersible particulate compositions for pulmonary administration to the respiratory tract for local or systemic therapy via aerosolization (page 8, lines 1 – 10). The compositions comprise a polyvalent cation such as calcium (page 8, line 28). Exemplary phospholipids include dipalmitoylphosphatidyl choline, disteroylphosphatidylcholine, etc. (page 9, lines 20+). The formulations may be used in conjunction with metered dose inhalers, dry powder inhalers, nebulizers, etc. (page 12, lines 18 – 27). The medicament is formulated in a way such that it readily disperses into discrete particles with a mass median diameter

from 0.5 to 20 μm (page 12, lines 28+). The compositions typically yield powders with bulk densities less than 0.5 g/cm^3, preferably less than 0.1 g/cm^3 (page 14, lines 12 – 20). The hollow/porous particulate compositions are preferably prepared by spray drying (page 15, lines 23+). In order to maximize dispersibility, dispersion stability, and optimize distribution upon administration, the mean geometric particle size of the particulate composition is preferably from 0.5 – 5 μm (page 20, lines 18+).

It is noted that Weers teaches that the active agent to be delivered may be a variety of drugs, and does not specifically exemplify or claim amphotericin as the bioactive agent which is employed.

Cicogna teaches the prophylactic efficacy of aerosol amphotericin lipid complexes in a rat model of pulmonary aspergillosis. Invasive pulmonary aspergillosis is a significant complication in immunocompromised patients. Intravenous amphotericin B is the standard treatment for invasive pulmonary aspergillosis, but the drug is toxic and is often poorly tolerated. Inhalation of drug aerosols, by yielding high drug concentrations in the lungs and decreasing the systemic drug burden, should maximize effectiveness and limit systemic toxicity. Aerosol amphotericin has been shown to efficiently deliver amphotericin to the lungs, while minimizing accumulation in other organs (page 259). Cicogna teaches an aerosolized amphotericin B lipid complex (aero-ABLC) to have higher and more prolonged levels of amphotericin compared with aerosolized amphotericin (aero-AmB) (page 261).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize spray-dried porous and/or hollow particulates comprising

amphotericin in combination with phospholipids, as taught by Weers, for pulmonary administration, because amphotericin was suggested as one of a variety of drugs which can be formulated as such for effective pulmonary drug delivery. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because Cicogna specifically teaches that aerosol delivery of phospholipid complexes of amphotericin are effective as prophylactic agents in reducing aspergillus infection. Both Weers and Cicogna are drawn to pulmonary drug delivery compositions and methods, thus they are clearly in the same field of endeavor. One of ordinary skill in the art would have been motivated to consider all of the pertinent prior art in the field of pulmonary drug delivery and drugs useful therefore when performing endeavors therein.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER